ISSN 0020-4412, Instruments and Experimental Techniques, 2018, Vol. 61, No. 5, pp. 745–750. © Pleiades Publishing, Ltd., 2018.
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PHYSICAL INSTRUMENTS FOR ECOLOGY, MEDICINE, AND BIOLOGY

A Method and a Device Prototype for Noninvasive Measurements of Blood Perfusion in a Tissue[1]

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Received August 8, 2017; in final form, March 7, 2018

Abstract—Noncoherent fluctuation spectroscopy (NFS) is described as an optical method for measuring the tissue blood perfusion. This method is based on the registration of low-frequency fluctuations of a backscattered signal from a tissue in the frequency range of 0–20 Hz. It allows the assessment of the blood-flow intensity in small blood vessels of the skin by calculating an integral parameter, the perfusion index, which is similar to that in the laser Doppler flowmetry (LDF) method. A device prototype in which LEDs at wavelengths of 568 and 808 nm are used in a miniature optical head was developed. The device makes it possible to perform diagnostics during the subject's motion via the use of LED light sources. It is shown that the NFS signal is comparable with the LDF signal. Thus, the NFS method can serve as an inexpensive alternative to the LDF method.

DOI: 10.1134/S0020441218050093

INTRODUCTION

The dynamic parameters of the blood circulation in small blood vessels of organs (arterioles, venules, capillaries, etc.), in particular, the blood flow or perfusion, are important physiological parameters in the evaluation of the functional state of human tissues and organs and are important for the detection of various dysfunctions, diseases, and pathological disorders [1]. Their evaluation in medicine is important both in an ordinary (normal) state of a tested person and when using various functional stress tests on the blood microcirculation system, that is, tests with occlusion, local heating, physical exercise, etc. [2]. Noninvasive spectrophotometric methods that allow long-term monitoring of the blood microcirculation parameters and the assessment of their changes during loading tests are promising methods for estimating the dynamic parameters of the blood microcirculation [3].

The method of laser Doppler flowmetry (LDF) allows one to obtain the most complete information on the blood-microcirculation parameters [4, 5]. The method uses laser illumination of a studied biological tissue and registration of backscattered radiation from the tissue. This radiation contains at least two components: the scattered radiation at the initial frequency of the probing laser from stationary inhomogeneities in the cell biotissue and the scattered radiation from moving blood components, erythrocytes with a Doppler frequency shift. When these signals are summed, they form low-frequency beats at the frequency ω [6]. The first moment of the spectral power density (SPD) of the photodetector photocurrent $P(\omega)$, which is normalized to a constant signal, allows the signal *Perf* to be obtained [7]:

$$Perf = \frac{k_0}{i_{DC}^2}\int_{\omega_1}^{\omega_2}\omega P(\omega)d\omega, \quad (1)$$

which is measured in arbitrary perfusion units and is proportional (with the proportionality factor k_0) to the flow of erythrocytes moving in vessels (to the perfusion of tissues with blood). In (1), ω_1 and ω_2 in commercial instruments are usually equal to 20 Hz and 20 kHz, respectively [8, 9], and i_{DC} is the average value of the recorded photocurrent. The integral parameter *Perf* is the microcirculation index/characteristic (in the Russian terminology), or the perfusion index/characteristic (in the English literature); to date, it is most informative in the functional diagnostics of the blood-microcirculation system and contains the frequency components of physiological blood-flow fluctuations: pulse waves, respiratory, myogenic, neurogenic, and endothelial waves [10].

However, as was shown in [11, 12], in addition to the Doppler component, the input LDF signal also contains an amplitude-modulated component, which is determined by various physiological processes in an organism, such as the rhythmic work of the heart,

[1] "Supplementary materials are available for this article at DOI 10.1134/S0020441218050093 and are accessible for authorized users".

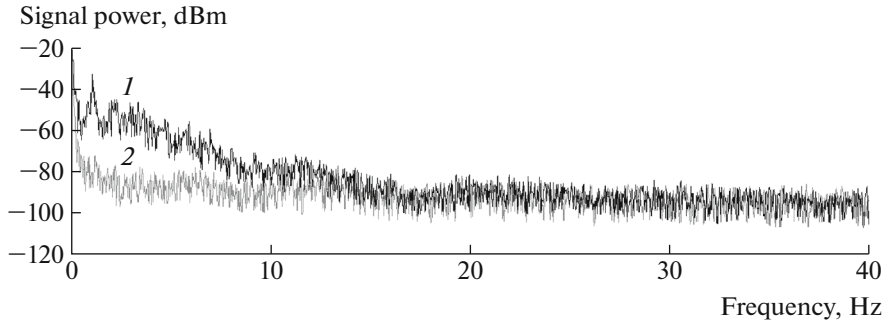

Fig. 1. The spectral density of the power of an amplitude-modulated signal that was recorded from the fingertip of a healthy volunteer in vivo (*1*) at rest and (*2*) at the moment of arterial blood-flow occlusion.

vasodilation and vasoconstriction of vessels, the tissue movement due to respiratory and circulatory regulation of the vascular bed, etc. In [13, 14], it was shown that the total SPD of the photocurrent $P(\omega)$ is a complex sum of components that are formed from the registration of different components of backscattered radiation: from stationary inhomogeneities inside the cell biotissue at the initial frequency of probing radiation and from moving shaped blood elements with a Doppler frequency shift and an amplitude modulation at different frequencies, as well as contributions from different beats of different components with an amplitude modulation and components with Doppler frequency shifts. Thus, if the backscattered radiation with amplitude modulations at different frequencies is registered and analyzed, the SPD of the total arising photocurrent can be used to calculate the perfusion index using (1), as in the LDF method. The objective of this study was to develop a method for measuring blood perfusion, which is based on this principle, and a device that performs this method.

THE MODEL OF MEASURING THE BLOOD PERFUSION

When light falls onto a tissue, part of it is absorbed by soft cell tissues, while the other part is absorbed by arterial and venous blood. The intensity of the signal due to tissue-backscattered and photodetector-registered radiation can be represented in the form

$$i(t) = i_{DC} + i_{AC}(t), \quad (2)$$

where i_{DC} is a constant signal that is formed due to light scattering in the skin and other underlying tissues and is independent of time, and $i_{AC}(t)$ is the variable amplitude-modulated signal that is formed by the absorption of light by blood chromophores and that depends on time due to changes in the blood volume in the microvascular bed of the skin.

Blood perfusion can be defined as the rate of change in the volume of blood in a tissue within a certain period of time [15]. Since blood moves nonuniformly, the rate of change in the blood volume in the tissue, in turn, is proportional to the amplitude of the signal, which represents the change in the level of volumetric tissue filling with blood, i.e., to the signal i_{AC} amplitude. Thus, by recording the amplitude of i_{AC}, one can evaluate the blood-perfusion level for some tissue region. Figure 1 shows the spectrum of the amplitude-modulated signal i_{AC}, obtained by illuminating the skin of a human finger with an IR LED at a wavelength of 808 nm at rest and upon blood-flow occlusion when the brachial artery is clamped. As seen in Fig. 1, the amplitude-modulated signal that is related with the blood flow has the frequency range of 0 to ~20 Hz. Consequently, this amplitude-modulated component of backscattered radiation carries useful information about the blood flow in the microvascular bed.

Thus, by illuminating the biological tissue with optical LED radiation and registering backscattered radiation in the frequency range of the amplitude modulation, beats, and other signal fluctuations from 0 to 20 Hz, the SPD of the total photocurrent can be used to calculate a certain integral perfusion index similar to the *Perf* index in expression (1). Let us call this method for measuring the blood-microcirculation flow noncoherent fluctuation spectroscopy (NFS). Thus, in the proposed method, the perfusion index is defined as the power of the variable signal component i_{AC} normalized to the power of the DC component i_{DC}:

$$Perf = \frac{k_0}{i_{DC}^2}\int_{\omega_1}^{\omega_2} P(\omega)d\omega, \quad (3)$$

where ω_1 and ω_2 are 0 and 20 Hz, respectively. In contrast to the photoplethysmography method, which is based on the registration of arterial blood-flow fluctuations in the frequency range of the i_{AC} signal from approximately 0.5 to 1.5–5 Hz [16–18], this method involves the registration of a signal associated with the blood flow in small vessels (arterioles, venules, capillaries, etc.) in the entire frequency range of the amplitude modulation, beats, and fluctuations from 0 to 20 Hz.

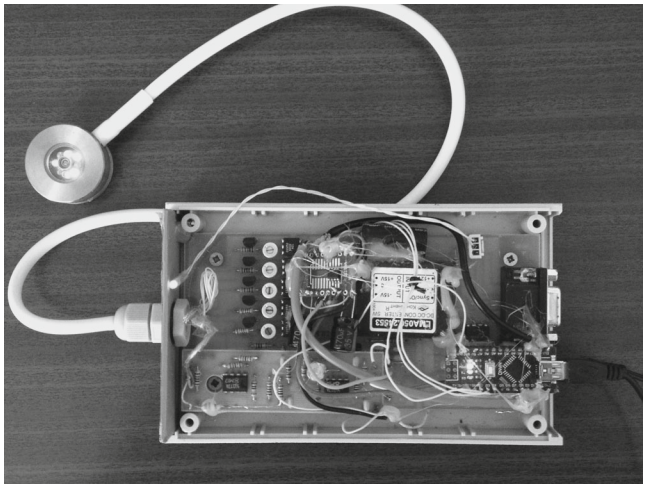

Fig. 2. The appearance of the developed device for measuring the skin blood flow.

A PROTOTYPE OF THE DEVICE

A device that performs the above method for measuring the blood perfusion was developed on the basis of a Spectrotest optical tissue oximeter and analyzer of volumetric capillary blood filling of biological tissues (NPP Tsiklon-Test, Fryazino, Moscow oblast) [19]. The appearance of the device is shown in Fig. 2, while its block diagram is shown in Fig. 3 [20].

The device consists of a radiation source (*RS*) for illuminating an examined biological tissue and a photodetector (*PD*) (a silicon photodiode) for registering backscattered radiation from the investigated biological tissue. The radiation source and the photodetector are located in the optical head (*OH*). The radiation source consists of six LEDs, three of which emit narrow-band radiation in the green spectral range at wavelengths of 560–580 nm (Fig. 4, *a*), while the other three emit narrow-band radiation in the near IR spectrum at wavelengths of 800–820 nm (Fig. 4, *b*). As the wavelength of tissue probing, it is necessary to use one of the isobestic points, at which the light absorption by oxyhemoglobin and deoxygemoglobin is the same, to prevent a difference in the measurements associated with different light transmittances by venous and arterial blood, because the total signal from blood is recorded in the device regardless of the percentage of oxyhemoglobin in it. Thus, isobestic points at 568 and 808 nm [21] were chosen as the wavelengths of the radiation sources.

In the optical head *OH* (Fig. 4), LEDs *a* and *b* are positioned radially around the photodetector *PD* at the distance $r = 3$ mm from its center at an identical distance from one another to provide uniform illumination of the biotissue volume around the *PD*. The LED outputs are set at the same level with the working surface of the photodetector to prevent the passage of light directly, bypassing the diagnosed tissue. At the same time, the design of the optical head itself is such that the possibility of mounting it on the human body with a strap or adhesive tape is provided, so that the working surfaces of the photodetector and the radiation sources touch the examined surface of the body. The depth of tissue probing is approximately 1–2 mm [22].

The device operates as follows. The control and synchronization unit (*CU*) forms rectangular control pulses at the operating frequency F_{op}, e.g., 320 Hz. The radiation sources (LEDs *a* and *b*) are switched on alternately during the action of this pulse (781.25 μs) at the moment of the arrival of the pulse from the control unit and illuminate the tested biotissue (skin) with their optical radiation, which is scattered and absorbed in the tissue; its backscattered components return from the tissue back to the surface and are registered by the photodetector *PD*. From its output, the signal is fed to a DC amplifier (DCA) (K140UD7), in which it is amplified, and then to the main information input of an analog-to-digital converter (*ADC*) (AD7680). The *ADC* operation is synchronized with the pulses

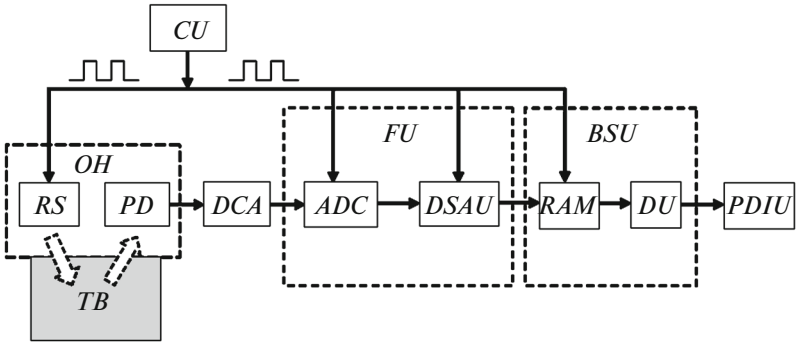

Fig. 3. The block diagram of the device for measuring the skin blood flow: (*OH*) optical head, (*RS*) LED radiation source, (*PD*) photodetector, (*DCA*) direct-current amplifier, (*FU*) electronic filtering unit, (*ADC*) analog-to-digital converter, (*DSAU*) digitized-signal averaging unit, (*BSU*) background-illumination subtraction unit, (*RAM*) random-access memory, (*DU*) difference unit, (*PDIU*) perfusion-index determination and indication unit, (*CU*) control unit, and (*TB*) tested biotissue.

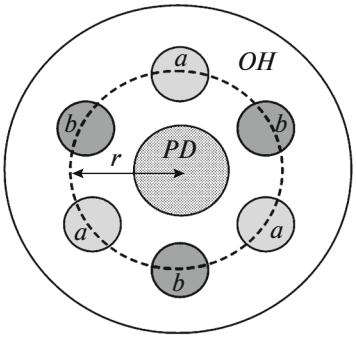

Fig. 4. The arrangement of the LED radiators (*a*, in the green spectral range of 560–580 nm and (*b*) in an IR range of 800–820 nm) and the photodetector *PD* in the optical head *OH* of the proposed device.

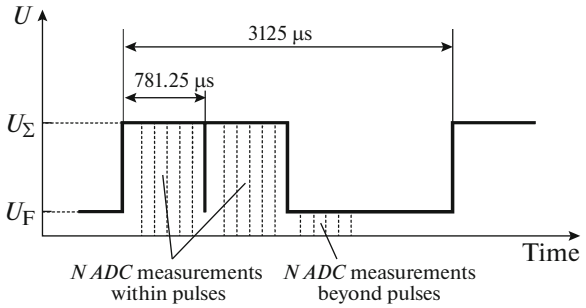

Fig. 5. The time diagram of the control pulses and the moments of signal digitization in the *ADC*.

that arrive at its synchronizing input from the control unit so that during the switching-on time of the group of LEDs, as well as during their switching-off time, the *ADC* has time to digitize the signal several (*N*) times, but not less than $N = 5$ (Fig. 5). The digitized *N* signal values during the action of the control pulse will correspond to the total useful signal with an admixture of the background illumination signal $U_{\Sigma i}$, while the digitized *N* signal values within the time when a control pulse is absent and the radiators are disabled, will correspond to the background illumination signal U_{Fi}, where $i = 1, 2, 3,..., N$.

Subsequently, synchronously with control pulses, $U_{\Sigma i}$ and U_{Fi} signals are averaged over *N* measured values (each in its cycle, at the instants when pulses act and are absent) in the digitized-signal averaging unit (DSAU) according to the formulas:

$$U_{\Sigma av} = \frac{1}{N}\sum_{i=1}^{i=N} U_{\Sigma i}, \quad (4)$$

$$U_{Fav} = \frac{1}{N}\sum_{i=1}^{i=N} U_{Fi}. \quad (5)$$

The found average values of $U_{\Sigma av}$ and U_{Fav} are then stored in their own cycles (at the instants when pulses act and are absent) in response to control pulses in a random access memory (*RAM),* which is the internal memory of an ATmega328P microcontroller (Atmel). In the difference unit (*DU*), the background illumination is compensated and the useful signal U_{us} is selected via subtraction of U_{Fav} from $U_{\Sigma av}$ at the moment of arrival of the next pulse by the formula

$$U_{us} = U_{\sum av} - U_{Fav}. \quad (6)$$

Thus, from the output of the difference unit (*DU*), a useful signal U_{us} that was cleared of background illumination arrives at the input of the perfusion-index determination and indication unit (*PDIU*). In this case, the applied procedure of multiple digitization and subsequent averaging is equivalent to the procedure of signal filtering at frequencies above F_{op} (above 320 Hz in this case). The quality of filtering will be determined by the number of digitizations *N*. As a result, the useful signal U_{us} will contain constant (i_{DC}) and variable (i_{AC}) components of the signal in the frequency range of 0–320 Hz, which, using the Nyquist theorem, allows one to analyze the signal frequency spectrum in the range from 0 to 160 Hz.

DIGITAL SIGNAL PROCESSING

In the perfusion-index determination and indication unit (*PDIU*) (Fig. 3), which runs in the LabView software environment, the useful signal U_{us} undergoes the final digital processing (see Fig. 6). The theory of the signal processing in this unit is based on the calculation of the rms value of the variable signal component [9, 23].

The signal is first filtered in a third-order bandpass filter (*BPF*) with the lower cutoff frequency $\omega_1 = 0.5$ Hz and the upper cutoff frequency $\omega_2 = 20$ Hz and is amplified (*A*); next, the rms signal value (U_{RMS}) is calculated in the RMS-DC converter (*Cnv*) with the window width $n = 640$ points. A signal from the *Cnv* output is smoothed in a filter (*SF*); subsequently, the signal power is calculated in a squaring unit (SU_1); finally, it is normalized to the power of the DC signal component (i_{DC}) in a divider (*Div*). The DC signal component is selected in the unit of digital frequency Fourier analysis (*DCEU*) as the zero term of the expansion into a Fourier series with a window width of $n = 320$ points and then is also squared in SU_2. Thus, the output perfusion signal *Perf* is formed at the divider output in accordance with formula (3). The signals received upon illumination of the biotissue with LEDs (green and IR) are processed simultaneously via two identical channels.

At the first stage of the experiments, the baseline level of the perfusion at the tips of the fingers of a healthy volunteer was recorded. The recording was carried out for 10 min, during which the hand of the

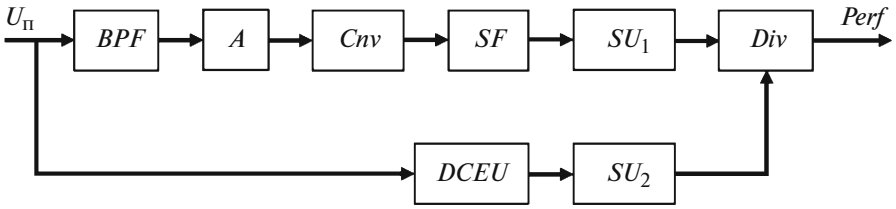

Fig. 6. The block diagram of the perfusion-index determination and indication unit: (*BPF*) bandpass filter, (*A*) amplifier, (*Cnv*) RMS-DC converter, (*SF*) smoothing filter, (SU_1, SU_2) squaring units, (*DCEU*) DC signal component extraction unit, and (*Div*) divider.

tested person was motionless on a table. The records of the perfusion index are shown in Fig. 7.

As seen in Fig. 7, the signals that were obtained by the two methods are very similar. Both the NFS signal and the LDF signal respond to involuntary sighs (marked with arrows).

CONCLUSIONS

In this study, we propose a method for measuring the skin microcirculatory blood flow in the form of noncoherent fluctuation spectroscopy based on the registration of low-frequency fluctuations of a backscattered signal from a microvascular bed in the frequency range from 0 to 20 Hz. The method allows one to estimate the intensity of the blood flow in small blood vessels of skin (arterioles, venules, capillaries, etc.) by calculating the integral parameter *Perf*, which is similar to the perfusion index in the laser Doppler flowmetry method. Based on this method for measuring the skin blood flow, a prototype of a device for two wavelengths (568 and 808 nm) was developed. Due to the different depths of tissue probing, a wavelength of 568 nm can be used to register the surface skin blood flow, while a wavelength of 808 nm is used for the analysis of deeper subcutaneous blood flow. LEDs were used as radiation sources in the proposed device. This makes it possible to eliminate the main disadvantages of the LDF method that are associated with the use of a laser to illuminate a biological tissue and an optical fiber to transport laser radiation to the biological tissue and back [24]. A fiber is very sensitive to even the slightest movements of a patient, which immediately lead to artifacts in the recorded data, thus not allowing dynamic observations to be performed during the patient's movement.

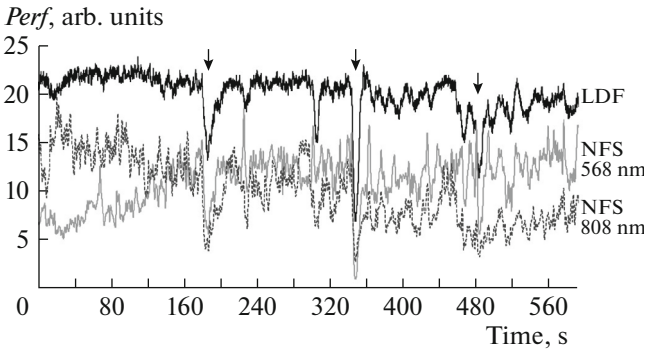

Fig. 7. The base records of the perfusion index *Perf* from the fingertips of the hand of the tested person that were obtained using the LDF and NFS methods. Arrows indicate the moments of involuntary sighs of the tested volunteer.

Due to the pulse operating mode of the LEDs, a single-channel signal-processing scheme is used in the device, which allows one to abandon the two-channel differential scheme of classical LDF devices with its intrinsic disadvantages [25]. The influence of the external background illumination on the recorded signal is compensated in the device. The miniature optical head can be attached motionlessly to a human body and move synchronously with the body, without creating mutual shifts of the body relative to the head and not preventing a free movement of the body. The device is suitable for the adequate functional diagnostics of a moving tested person. In the future, the head can be equipped with wireless communication with the remainder of the device; as an example, Bluetooth can be used as a communication medium, thus imparting even more freedom of movement to the tested person and making wearable individual systems for daily monitoring of the blood perfusion index of tissues possible.

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Translated by A. Seferov

Supplementary materials to the

METHOD AND DEVICE PROTOTYPE FOR NONINVASIVE MEASUREMENT OF BLOOD PERFUSION IN THE TISSUE

Experiments

The developed device based on the non-coherent fluctuation spectroscopy (n.f.s.) method was tested on 4 healthy volunteers. The optical head of the device was fixed on the tip of middle finger of the subject's hand. For comparison with the laser Doppler flowmetry (l.d.f.) method the fiber optic probe of the l.d.f. device "LAKK-02" (LAZMA Ltd., RF) was fixed on the tip of ring finger (see Fig. 8). The operating wavelength of the "LAKK-02" laser is 1064 nm. The n.f.s. and l.d.f. signals were recorded simultaneously during the measurements.

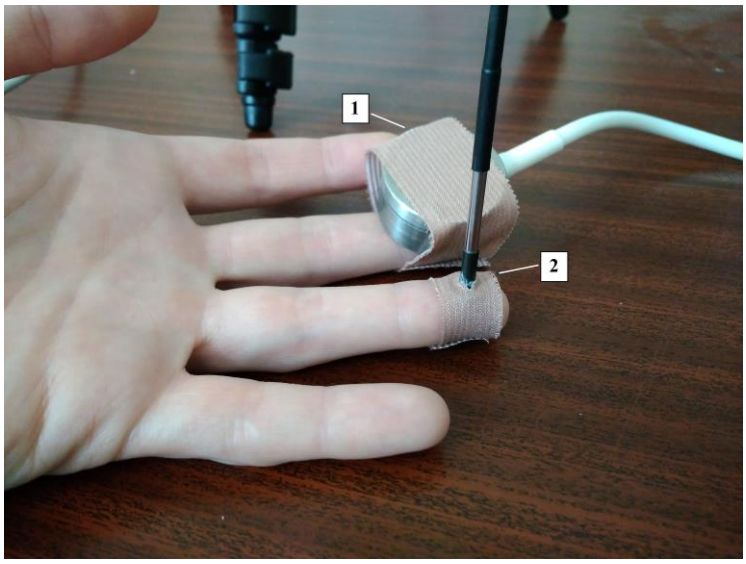


Fig. 8. Placement of the optical sensor of the developed device (1) and fiber probe of the l.d.f. instrument "LAKK-02" (2) on the subject's hand during the measurements.

Recording of the base blood flow

The base records of the blood perfusion obtained by the l.d.f. and n.f.s. methods are presented in Fig. 7. A standard tool for studying l.d.f. signals is spectral analysis based on the wavelet transform [26, 27]. It allows to analyze the low-frequency blood flow oscillations in the

cardiac (C), respiratory (R), myogenic (M), neurogenic (N) and endothelial (E) frequency ranges [26]. So, the wavelet analysis of the base records of the perfusion was performed (see Fig. 9).

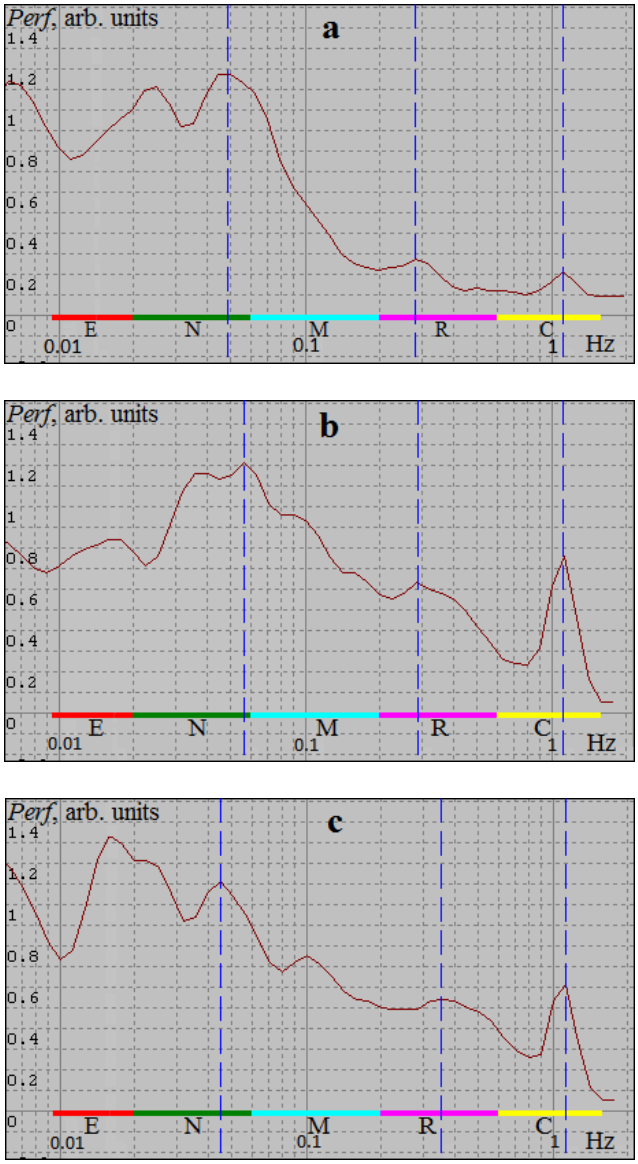


Fig. 9. Wavelet spectra of the base records of the l.d.f. (a), n.f.s. at 568 nm (b) and 808 nm (c) signals. Dotted lines show local maximums of the spectrum in the respective frequency ranges.

As can be seen in Fig. 9, in the base records of the n.f.s. and l.d.f. signals there are pronounced low-frequency oscillations, in this case cardiac, respiratory and neurogenic. Herewith, the amplitudes of cardiac and respiratory oscillations in the n.f.s. signals are

approximately 3 times larger than the corresponding amplitudes in the l.d.f. signal. Amplitudes and frequencies of these rhythms of all three signals for comparison are summarized in Table 1.

Table 1. Amplitude and frequencies of low-frequency rhythms of base blood flow by results of wavelet analysis of the l.d.f. and n.f.s. signals.

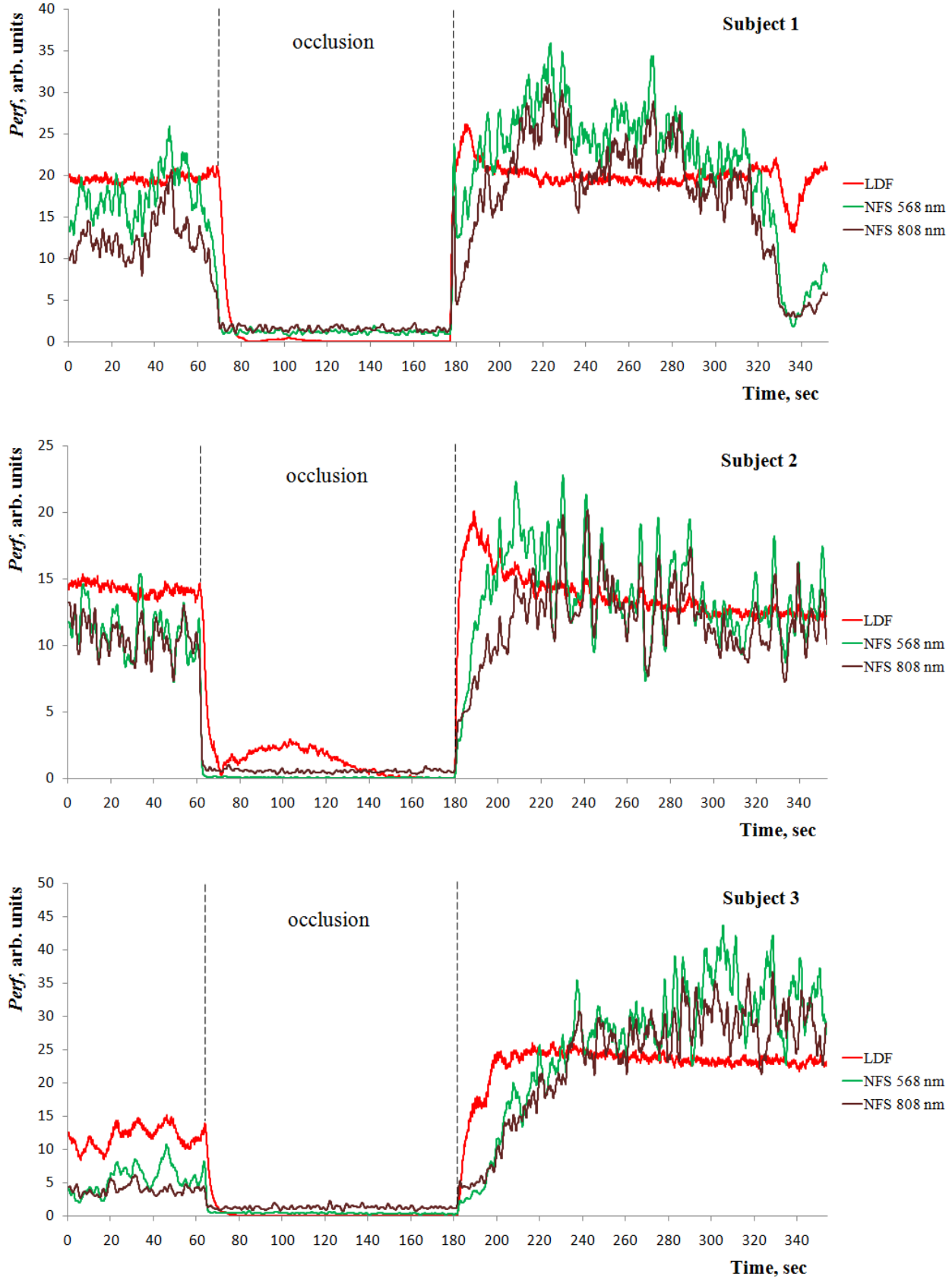
Rhythm		Signal		
		l.d.f.	n.f.s. 568 nm	n.f.s. 808 nm
C	Frequency, Hz	1.12	1.12	1.13
	Amplitude, arb. units	0.21	0.74	0.61
R	Frequency, Hz	0.28	0.29	0.35
	Amplitude, arb. units	0.26	0.62	0.53
N	Frequency, Hz	0.05	0.06	0.05
	Amplitude, arb. units	1.17	1.20	1.10

As seen from Table 1, the frequencies of the cardiac, respiratory and neurogenic oscillations in the l.d.f. and n.f.s. signals are almost the same. Similar results were also obtained in [28].

Arterial occlusion test

In the second stage, the arterial occlusion test was performed on 4 subjects to evaluate the change in the n.f.s. signal in response to various loads on the blood microcirculation system. Occlusion of arterial blood flow was performed using a standard blood pressure cuff which was inflated to the level of 300 mm. Hg. The recording protocol of the occlusion test was the following: 1st minute - the base blood flow; 2nd and 3rd minutes - the occlusion of blood flow;

4th, 5th and 6th minutes - after occlusion. The l.d.f. and n.f.s. perfusion signals during occlusion are presented in Fig. 10.



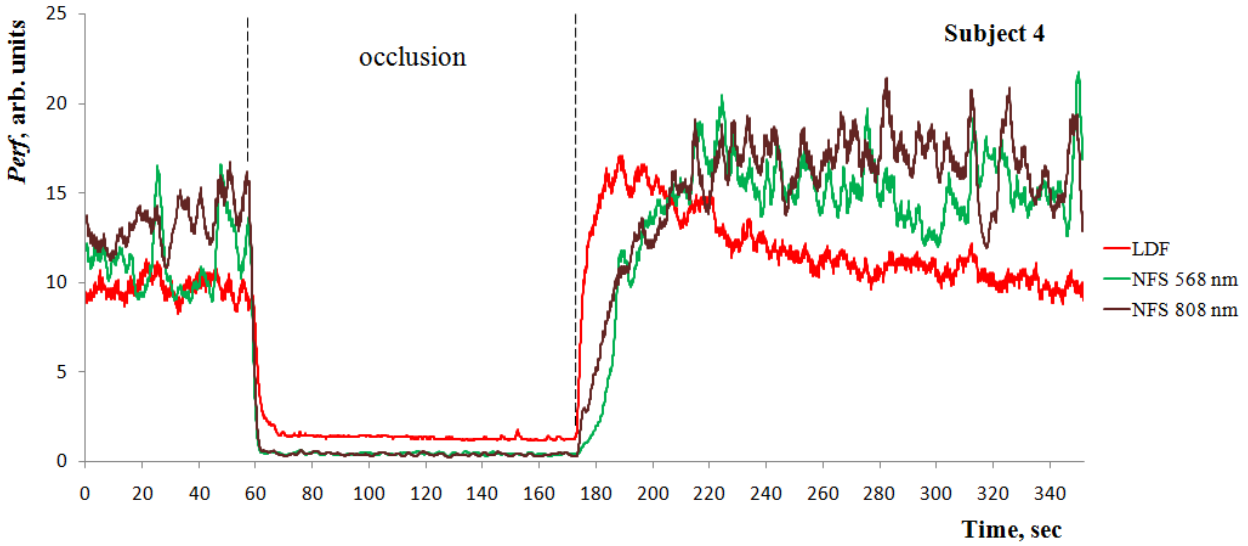


Fig. 10. The l.d.f. and n.f.s. signals recorded during arterial occlusion test for four subjects.

As can be seen in Fig. 10, the n.f.s. signal similar to the l.d.f. signal drops to about zero during occlusion and significantly increases after cuff deflation during post-occlusive reactive hyperemia (p.o.r.h.). In p.o.r.h. the n.f.s. signal increases approximately to the same maximum level as the l.d.f. signal but with a greater time delay. Similar results were obtained in [15, 29, 30] in which such parameters as blood perfusion and blood pulsation amplitude using by photoplethysmography and pulse pressure using by plethysmography were studied during arterial occlusion. The correlation between l.d.f. and n.f.s. signals was estimated by calculating the Pearson coefficients. The results are presented in Table 2.

Table 2. The correlation between l.d.f. and n.f.s. signals during occlusion test for 4 subjects.

Subject's number	The Pearson correlation coefficient, rel. units		
	$R_{\text{l.d.f.,n.f.s.568}}$	$R_{\text{l.d.f.,n.f.s.808}}$	$R_{\text{n.f.s.568,n.f.s.808}}$
1	0.83	0.75	0.98
2	0.89	0.88	0.97
3	0.88	0.87	0.98
4	0.86	0.86	0.97

The correlation between l.d.f. and n.f.s signals is slightly higher at a wavelength of 568 nm. In general, the correlation of l.d.f. and n.f.s signals for occlusion test is quite strong for both wavelengths. This suggests that the registration of low-frequency blood volume fluctuations also carries information about the level of blood perfusion in the tissue.

Conclusions

Testing of the developed device was carried out in comparison with the l.d.f. method on 4 healthy volunteers. It was shown that the n.f.s. signal for wavelengths of 568 and 808 nm is comparable with the l.d.f. signal. It carries information about the level of blood perfusion and the regulation rhythms of microvascular blood flow (endothelial, neurogenic, myogenic, etc.). On an example of the test with arterial occlusion it was shown that n.f.s. signal responds to load incentives, thus, is an informative in the assessment of the functional state of the blood microcirculation. High correlation between n.f.s. and l.d.f. signals by results of occlusion test was obtained (R = 0.8–0.9 rel. units). Further comparative studies of these two signals are required.

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